REMARKS

Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

Claims 1-49, 51-55, 58-60, 63-76, 88-124, 127-143 and 145-147 are pending. Claims 86 and 144 are cancelled without prejudice or disclaimer. Claim 1 is amended herein to clearly state that, as argued previously, the molecular weight of hybridized nucleic acid in the array is determined. Antecedent basis is found within claim 1, and basis for the amendment if found throughout the specification (*e.g.*, see page 14, lines 1-3). Therefore, no new matter is added.

I. THE REJECTIONS OF CLAIMS 1-17, 19-27, 29-39, 43-49, 51-54, 58-60, 63-70, 73-76, 86, 88-124 AND 127-145 UNDER 35 U.S.C. §103(a)

Claims 1-17, 19-27, 29-33, 35-37, 43-49, 51, 52, 54, 64-70, 73-76, 124 and 127 are rejected under 35 U.S.C. §103(a) over Köster (WO 94/16101) in view of Cantor (US 5,503,980) on page 2 of the Office Action, claim 34 is rejected under 35 U.S.C. §103(a) over Köster (WO 94/16101) in view of Cantor (US 5,503,980) on page 9 of the Office Action, and claims 38, 39, 53, 58-60, 63, 86, 88, 89-124 and 128-145 are rejected under 35 U.S.C. §103(a) over Köster (WO 94/16101) in view of Cantor (US 5,503,980) on page 11 of the Office Action. The rejections are respectfully traversed.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

A. Rejection of Claims 1-17, 19-27, 29-33, 35-39, 43-54, 58-60, 63-70, 73-76, 88-123 and 128

The combination of the teachings of Köster with the teachings of Cantor does not result in the instantly claimed methods.

Claim 1 and its dependent claims require determining molecular weights of hybridized nucleic acids in the array to identify hybridized probes. Applicant previously argued that the combination of the teaching of Köster and Cantor did not teach every element of the claimed methods, which includes determining molecular weights of hybridized nucleic acids in the array to identify hybridized probes. In response to Applicant's previous arguments, the Examiner states that Köster is not relied upon for the teaching of probe hybridization but for the extensive teaching with respect to using mass labels for sequencing and that Cantor is relied upon for the teaching of probe hybridization. The Examiner also states that Applicant's previous argument that Cantor does not teach detecting hybrids based upon molecular weight

of the hybrids is not persuasive because "Cantor is not relied upon for teaching the use of mass labels for detection but rather Köster is relied upon for this teaching" (see page 14 of the Action). Applicant respectfully submits that the instant method does not rely on using mass labels for sequencing. The instant methods of determining the sequence of a target nucleic acid includes as an element identifying hybridized probes in the array by determining molecular weights of hybridized nucleic acids in the target array.

Thus, it is irrelevant to the instant claims that Köster teaches using mass labels for sequencing and that Cantor teaches probe hybridization and sequence determination that includes detecting and locating a label. The question is whether the combination of the teachings of Köster and Cantor results in every element of the claimed method. Applicant respectfully submits that combining the teachings of Köster and Cantor does not result in a method for sequencing a target nucleic acid that includes identifying hybridized probes in the array by determining the molecular weight of the hybridized probes.

Köster teaches using base-specific chain termination (Sanger sequencing) to generate a set of nested fragments of a target nucleic acid and using mass spectrometry to analyze the nested fragments via their different molecular masses. In embodiments of Köster in which the nested fragments are attached to a solid support via Watson-Crick base pairing to a solid support-bound oligonucleotide, Köster teaches that the duplex formed between the fragment and the solid support-bound oligonucleotide will be cleaved by the influence of the mass spectrometer and that the resulting desorbed nucleic acid fragment is analyzed (*e.g.*, see page 14, lines 1-34, especially lines 33-34). Thus, Köster does not teach or suggest determining molecular weights of the hybridized nucleic acid molecules in the array. Instead, Köster teaches determining molecular weights of desorbed single-chain nucleic acid fragments or tag oligonucleotides. An embodiment of Köster is shown in Fig. 1, which is a representation of a process to generate the samples to be analyzed by mass spectrometry. As shown in Fig. 1, the single-chain Sanger nested fragments are cleaved off the support and presented for mass spectrometric analysis. Köster teaches that comparison of the mass difference measured between the nested fragments with the known masses of each chain-terminating nucleotide allows the sequence of each fragment to be determined. Based upon the mass of the fragments, the fragments are aligned and the sequences are determined. The method does not include determining molecular weights of hybridized nucleic acids in the array. Köster does not teach or suggest identifying hybridized probes in an array based upon molecular weight of the hybridized nucleic acids.

Cantor does not teach the elements missing from Köster. The method of Cantor relies upon labeling the target nucleic acid and detection of the label. There is no teaching or suggestion in Cantor of identifying hybridized probes in an array by determining the molecular weights of the hybridized nucleic acids in the target array. In the method of Cantor, the sequence is determined based upon detecting a label and determining the location of label, such as the determination of positional information using the ratio of internal label to terminal label. In the methods of Cantor, a label is detected. Cantor does not teach or suggest determining molecular weights of hybridized nucleic acid in the target array to identify hybridized probes, which is an element of the instant claims. As discussed above, Köster does not teach or suggest determining molecular weights of hybridized nucleic acid in the target array to identify hybridized probes. Hence, Cantor does not teach or suggest the subject matter missing from Köster. Thus, the combination of Köster and Cantor does not teach or suggest every element of claim 1. Claims 2-17, 19-27, 29-33, 35-39, 43-54, 58-60, 63-70, 73-76, 88-123 and 128 ultimately depend from claim 1 and include the limitations thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness for claims 1-17, 19-27, 29-33, 35-39, 43-54, 58-60, 63-70, 73-76, 88-123 and 128.

B. The Rejection of Claims 124, 127, 129 and 144-147

Claims 124, 129 and 144-147 are rejected under 35 U.S.C. § 103(a) over Köster (WO 94/16101) in view of Cantor (U.S. 5,503,980), because Köster allegedly teaches every element of the claims except probes that include a double-stranded portion and a single-stranded portion, probes having 10-1,000 nucleotides or having a variable region of about 4-20 nucleotides, arrays including 10^4 or more different members or arrays of probes having sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination, but Cantor allegedly cures these defects. This rejection is respectfully traversed.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Köster with the teachings of Cantor does not result in the arrays and systems of claims 124, 127, 129 and 144-147

The array of claim 124 requires that each probe includes a single-stranded portion and a constant double-stranded portion and that the array includes a collection of probes with sufficient sequence diversity in the variable region to hybridize to all of the target nucleic acid

molecule. The array of claim 124 also includes as an element that the array includes a nucleic acid probe **having at least one mass-modifying functionality** that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

As recognized by the Examiner on page 12 of the Action, Köster does not teach or suggest an array of nucleic acid probes where each probe includes a single-stranded portion and a constant double-stranded portion, or an array of probes having sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination, or probes that are about 10 to about 1000 nucleotides in length, or probes that include a variable region, or probes with a variable region of about 4-20 nucleotides in length. Further, Applicant respectfully submits that Köster does not teach or suggest an array of probes that includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Köster teaches that mass modifications may be introduced into the nested fragments via an oligonucleotide primer, chain-terminating nucleoside triphosphates and/or chain-elongating nucleoside triphosphates. Köster also teaches that tag specific probes with mass differentiated molecular weights may be used and that the tag specific probes can be detected. The tag specific probes of Köster are specific oligonucleotides that hybridize to specific tag sequences within each of the nested fragment families. Köster does not teach or suggest an array of tag specific probes. Further, Köster analyzes the desorbed nested fragments, not the probes of the array. Hence, Köster does not teach or suggest that the probes of the array include at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry.

Cantor does teach or suggest all of the elements missing from Köster. For example, Cantor does not teach or suggest an array that includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Cantor does not teach or suggest including in its array a mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Thus, even if Cantor teaches various lengths of probes, various lengths of variable regions within its probes and that fragments of nucleic acids comprise greater than 10^4 different members, Cantor does not teach or suggest all the elements missing from the teaching of Köster.

Thus, combining the teachings of Köster and Cantor does not result in every element of the claimed array of nucleic acid probes, which includes a nucleic acid probe having at least one

mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Claim 127 recites a system that includes a mass spectrometer, a computer and the array of claim 124. As discussed above, combining the teachings of Köster and Cantor does not teach or suggest the array of claim 124, which includes a nucleic acid probe having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Hence, the combination of the teachings of Köster and Cantor does not result in the system of claim 127. Thus, combining the teachings of Köster and Cantor does not result in every element of the claimed arrays and system of claims 124, 127, 129 and 144-147. Therefore, the Examiner has failed to set forth a *prima facie case* of obviousness.

II. THE REJECTION OF CLAIM 28 UNDER 35 U.S.C. §103(a)

Claim 28 is rejected under 35 U.S.C. §103(a) over Köster and Cantor in view of Weiss (U.S. 6,025,193) because the combination of Köster and Cantor allegedly teaches all elements of claim 28 except generation of thiol moieties by using Beucage reagent, but Weiss allegedly cures this defect. This rejection is respectfully traversed.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Köster and Cantor with the teachings of Weiss does not result in the instantly claimed methods.

As discussed above, the combination of the teachings of Köster and Cantor does not teach or suggest a method for sequencing a target nucleic acid that includes as elements identifying hybridized probes in the array by determining the molecular weight of the hybridized probes, and based on the hybridized probes, determining the sequence of the target nucleic acid. Claim 28 depends from claim 1 and includes every limitation thereof. Accordingly, the combination of the teachings of Köster and Cantor does not teach or suggest every element of claim 28.

Weiss does not teach or suggest the subject matter missing from the combination of the teachings of Köster and Cantor. Weiss does not teach or suggest identifying hybridized probes in an array by determining the molecular weight of the hybridized probes, and based on the hybridized probes, determining the sequence of the target nucleic acid. Thus, even if Weiss teaches generating thiol moieties using Beucage reagent, Weiss fails to cure the deficiencies in the combination of the teachings of Köster and Cantor because Weiss does not teach or suggest

the elements of the claimed subject matter missing from the combination of the teachings of Köster and Cantor.

None of Köster, Cantor nor Weiss, individually nor in any combination, teaches or suggests a method for sequencing a target nucleic acid that includes as an element determining molecular weights of hybridized nucleic acids in the target array to identify hybridized probes. Thus, combining the teachings of Köster and Cantor with the teachings of Weiss does not result in the instantly claimed method of claim 28. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

III. THE REJECTION OF CLAIMS 71 AND 72 UNDER 35 U.S.C. §103(a)

Claims 71 and 72 are rejected under 35 U.S.C. §103 as being unpatentable over Köster and Cantor in view of Sanghvi *et al.* (U.S. Patent No. 6,214,551) because the combination of the teachings of Köster and Cantor allegedly teaches all elements of the claims except that the selectively releasable bond is 4,4'-dimethoxy-trityl or a derivative thereof, and Sanghvi *et al.* allegedly cures this defect. The Examiner contends that Sanghvi *et al.* teaches the selectively releasable bond 4,4'-dimethoxytrityl or a derivative thereof, and argues that although the reference does not teach the derivative 3 or 4 [bis-(4-methoxy-phenyl)]-methyl-benzoic acid in particular, Sanghvi *et al.* teaches equivalent compounds and derivatives used for the same purpose. This rejection is respectfully traversed.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Köster and Cantor with the teachings of Sanghvi *et al.* does not result in the instantly claimed methods.

Claims 71 and 72 ultimately depend from claim 1 and are directed to embodiments thereof. Thus, claims 71 and 72 include every limitation of claim 1. As discussed above, the combination of the teachings of Köster and Cantor does not teach or suggest methods for sequencing a target nucleic acid that include as an element determining molecular weights of hybridized nucleic acids in the target array to identify hybridized probes. Sanghvi *et al.* does not cure this defect. Sanghvi *et al.* does not teach or suggest sequencing a nucleic acid by hybridizing fragmented target nucleic acid to an array as claimed and determining molecular weights of hybridized nucleic acids in the target array to identify hybridized probes. Hence, Sanghvi *et al.* does not teach or suggest the elements missing from the combined teachings of Köster and Cantor.

Further, Claim 71 is directed to an embodiment where each probe is attached to a solid support by a selectively releasable bond that includes 4, 4'-dimethoxytrityl or a derivative thereof, and claim 72 specifies the derivatives of 4, 4'-dimethoxytrityl. Sanghvi *et al.* does not teach or suggest selectively attaching a nucleic acid probe to a solid support via releasable bonds containing 4,4'-dimethoxytrityl or a derivative thereof. Sanghvi *et al.* teaches the use of dimethoxytrityl groups as a blocking group during nucleoside polymerization. In Example 81, Sanghvi *et al.* teaches that an oligonucleotide is tethered to a solid support via its 3' hydroxyl group, not via a dimethoxytrityl group. The Examiner cites col. 59, lines 3-32 of Sanghvi *et al.* to support the allegation that the reference teaches 4,4'-dimethoxytrityl as a selectively releasable bond attaching a probe to a solid support. The recited section of Sanghvi *et al.* states:

> The dimeric oligonucleoside 58 will be utilized as building block units in a conventional oligonucleotide solid support synthesis as per the procedure of Example 80. For the purpose of illustration a polymer incorporating seven nucleosides is described. A first unit of the dimeric oligonucleoside 58 will be coupled to a first cytidine nucleoside **tethered to a solid support via its 3' hydroxyl group** and having a free 5' hydroxyl group. After attachment of the first unit of compound 58 to the support, the 5'-dimethoxytrityl group of that first compound 58 unit will be removed in the normal manner. A second compound 58 unit will then be coupled via its β-cyanoethyl-N-diisopropylphosphiryl group to the first compound 58 unit using normal phosphoramidate chemistry. This forms a conventional phosphodiester bond between the first and second compound 58 units and elongates the polymer by two nucleosides (or one oligonucleoside dimer unit). The **dimethoxytrityl blocking group** from the second compound 58 unit will be removed in the normal manner and the polymer elongated by a further dimeric unit of compound 58. As with addition of the first and second dimeric units, the third unit of compound 58 is coupled to the second via conventional phosphoramidite procedures. The addition of the third unit of compound 58 completes the desired length and base sequence. This polymer has a backbone of alternating normal phosphodiester linkages and the methyl-(iminooxymethylene) linkages of compound 58. **The 5' terminal dimethoxytrityl group of the third compound 58 unit will be removed in the normal manner** followed by release of the polymer from the solid support, also in the normal manner. ... [emphasis added]

There is no teaching or suggestion in Sanghvi *et al.* that a dimethoxytrityl group is a selectively reversible bond for attaching a nucleic acid molecule to a solid support. Instead, Sanghvi *et al.* teaches that dimethoxytrityl groups are useful for protecting intermediates during synthesis, especially as a hydroxyl protecting group (see col. 15, lines 8-19). Sanghvi *et al.* does not teach or suggest any of 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-hydroxymethyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-chloromethyl-benzoic acid as a selectively releasable bond and comprises 4, 4'-dimethoxytrityl or a derivative

thereof. Thus, the combination of the teachings of Köster and Cantor with the teachings of Sanghvi *et al.* does not teach or suggest all the elements of the methods of claims 71 and 72.

None of Köster, Cantor nor Sanghvi *et al.*, alone or in any combination, teaches or suggests a method for sequencing a target nucleic acid that includes as an element determining molecular weights of hybridized nucleic acids in the target array to identify hybridized probes. Further, none of Köster, Cantor nor Sanghvi *et al.*, alone or in any combination, teaches or suggests the limitations of claims 71 and 72. Thus, combining the teachings of Köster and Sanghvi *et al.* does not result in the instantly claimed methods of claims 71 and 72. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the above remarks and amendment, reconsideration and withdrawal of the rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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